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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/852,547	05/10/2001	David A. Sirbasku	1944-00800	6474

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/852,547	SIRBASKU, DAVID A.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 95 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 95 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 24, 2006 has been entered.

Claims 1-8, 12-15, 17-20, 66-69, 71, 73-79, 81-90, 92-94 have been canceled. Claim 95 has been added and is under consideration.

Sections of Title 35, U.S. Code, not found in this action, can be found in a prior action.

It is noted that on page 10, lines 19-21 defines immunoglobulin inhibitor as one or more of IgA, IgM and IgG1 which provide support for new claim 95, because "one or more" includes all three of IgA, IgM and IgG1.

Claim 95 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.. The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The instant claim requires that a decrease in the level of cumulative secretory immunoglobulins in a secreted body fluid obtained from a subject is indicative of a susceptibility to the development of an estrogen hormone responsive cancer in said subject. Predicting a susceptibility requires that the susceptibility determination be done before the subject has actually developed said cancer. The claim lacks of enablement for quantitating or detecting an immunoglobulin inhibitor of steroid hormone responsive cell growth in a specimen of body fluid or secretion because the specification provides no reasonable expectation of success of detecting an increase in secretory immunoglobulin secretion over the background of natural secretory immunoglobulin secretion in a subject who has yet to develop a cancer. The specification states on page 10, [0018] that for "purpose of this disclosure, the term "immunoglobulin inhibitor" refers to a secretory immunoglobulin, preferably on of the secretory immunoglobulins IgA, IgM and Ig1 that is active for inhibiting proliferation of a steroid hormone responsive cancer cell. The specification bases the instant claims on the premise that measurement of said secretory immunoglobulins would then be diagnostic for inhibition of steroid responsive cell growth and that decreased levels of said immunoglobulins would then be indicative of decreased inhibition of said cell growth. The specification teaches that the secretory immunoglobulin system decreases activity with age. This is a general teaching dependent upon the averaging of multiple measurements of secretory immunoglobulins over a period of time encompassing years. However, it is known in the art that levels of IgA, the major secretory immunoglobulin, vary as a function of time of day, as well as within a year, and large variations between healthy subjects is documented (Garde et al, Clinical Chemistry, 2000, Vol. 46, pp. 551-559, cited in a previous action). The art also teaches that levels of secretory IgA is hormonally regulated in women and thus variable over the course of a menstrual cycle (Gomez et al, Amer J Reproduc Immunol, 1993, Vol. 29, pp. 219-223, cited in a previous action). It would be reasonable to conclude that the level of the other types of secretory immunoglobulins would also vary as a function of the exposure of an individual to exogenous antigens or substances provoking an immune reaction. Thus, it would be reasonable to conclude that the measurement of secretory immunoglobulins in a single sample would not be representative of the average

level of secretory immunoglobulins present within an individual during the course of a year or more. Given that the art teaches that the level of IgA, the major secretory immunoglobulin, varies both positively and negatively with time in a healthy individual and also varies between individual subjects and thus supports the conclusion that the level of other secretory immunoglobulins also vary with time by both increasing and decreasing; and given the lack of teachings in the specification regarding ranges or levels of secretory immunoglobulins that were indicative of normal individual versus individuals having a steroid hormone responsive cancer, one of skill in the art would be subject to undue experimentation in order to make and use the claimed methods relying on correlating the levels of secretory immunoglobulins with the presence or susceptibility to steroid hormone responsive cancer. Further, Sullivan et al (Immunology, 1983, Vol. 49, pp. 379-386) observe that the transudation of IgA in the uterus is mediated through the hormonal control of secretory component (page 380, first column, lines 23-29), but that the estrodiol accumulation of secretory component appears to be independent of IgA, because of the demonstration that dexamethasone suppressed IgA accumulation but not secretory protein accumulation (page 379, first column, lines 14-18). Notably, Sullivan et al state that following estradiol treatment, the source of uterine IgG appears to be plasma.

Hurlimann et al (Virchows Arch A Path Anat and Histol, 1978, Vol. 377, pp. 211-223) observe that in human biopsies of the endometrium that the endometrium did not synthesize immunoglobulins; secretory component was synthesized only by endometrial tissue in the secretory phase and by some carcinomas (Summary, lines 13-16). Hurlimann et al observe that there is no relationship between the production of secretory component and the presence of IgA plasmacytes which localize as a result of immunologic influences within the tissues studied (summary, lines 16-19), thus lending credence to the examiners position that variable immunological influences will cause fluctuations in the levels of the secretory immunoglobulins and that there is no reasonable expectation of success of being able to discern a level of secretory immunoglobulins attributable to increased risk of developing a hormonally responsive cancer in a mucosal epithelium over the level of secretory immunoglobulins being driven by the normal

immune response. Hurlimann et al disclose that in cervical tissues without a pathologic lesion exhibited few plasmacytes around glands and under the surface epithelium, and that culturing of the samples in vitro led to the identification of a very low level of synthesized immunoglobulins within the tissue (page 213, under the heading "Cervical Tissues without Lesion"). Hurlimann et al disclose that a low level of immunoglobulin synthesis could be detected by the culturing of neoplastic cervical tissue and that said tissue also showed few plasmacytes (page 214, under the heading of "Cervical Tissues with Metasplasia", in contrast to cervical neoplasia where the synthesis of IgG and IgA was marked and correlated with the presence of numerous IgG and IgA plasmacytes (page 215-216, under the heading "Carcinoma in Situ"). Hurlimann et al disclose that in the culturing of endometrial carcinoma biopsy samples the numerous IgG plasmacytes demonstrated immunoglobulin synthesis (page 219, under the heading of "Carcinoma"). Hurlimann et al conclude that secretory component is synthesized in excess when compared to the synthesis of IgA (page 219, lines 18-21 under the heading "Discussion"). Hurlimann et al disclose that although IgA synthesis in the samples examined is decreased in the age group between 44-68 years, loss of IgA synthesis is replaced by IgG synthesis (page 219, lines 27-35, under the heading of "Discussion"). Thus, it can be concluded that the transcytosis of secretory immunoglobulin is dependent upon the presence of local plasmacytes or the presence of an immunoglobulin in the serum. Further, Fudenberg et al (Basic and Clinical Immunology, 1978, page 326, pp. 324-328) teach that overall serum concentrations of IgG and IgA tend to increase with age whereas serum IgM tends to decrease (especially, page 326, second column, lines 9-10). Therefore, one of skill in the art would not conclude that persons of advancing age were deficient in IgG or IgA in serum levels, or IgG in mucosal levels.

Richarson et al (Journal of Steroid Biochemistry and Molecular Biology, 1993, Vol. 47, pp. 143-149) disclose that Il-6 and IFN-gamma in conjunction with estrogen resulted in an increase of both secretory component and IgA levels in uterine secretions in rat uteri and concluded that the regulation of secretory component is complex because it is controlled by the interactions of cytokines and sex hormones through both autocrine and paracrine effects (page 132, second column, lines 12-22). Brandtzaeg et al (In:

Developments in Biological Standarization, Brown and Haaheim, Ed.s, March 1998, Vol. 92, pp. 93-108) teach that secretory component can be up-regulated by IFN-gamma, Il-4 and TNF-alpha (pages 95-96, bridging sentence) which corroborates the teachings of Richardson et al. Verrijdt et al (Biochem Soc Transactions, 1997 May, Vol. 25, page 186S) report that human secretory component gene expression is under the influence of TNF-alpha, IFN-gamma, TGF-beta, glucocorticoids, estrogens and androgens, but the influence of estrogen appears to be opposed in the mammary gland and in the uterus (column 1, first paragraph). It is noted that the instant claims are broadly drawn to encompass the prediction of susceptibility to any type of mucosal epithelial cancer, not just breast.

Thus, the art teaches that the level of secretory immunoglobulins are control by a multiplicity of factors as evidenced by the discussion above. The claims require that a prediction of susceptibility be made based on level of secretory immunoglobulins in the bodily fluids of a subject before said subject actually develops a estrogen responsive cancer in a mucosal epithelium. for the reasons set froth above, and the lack of objective evidence in the specification or any art of record, the examiner maintains that one of skill in the art would be subject to undue experimentation in order to make the correlation between susceptibility to a estrogen response cancer and the level of secretory immunoglobulins, the levels of which the art teaches fluctuate in response to a multitude of factors unrelated to cancer susceptibility.

In example 22 of the specification it is stated:

0652] The subclasses of human IgG are IgG1, IgG2, IgG 3 and IgG4. They are formed with both .lambda. and .kappa. light chains. A series of studies was performed, and it was found that with human breast cancer cells, only IgG1.kappa. was a significant estrogen reversible inhibitor. FIG. 120 shows a comparison of its activity to human pIgA and pIgM. At 40 .mu.g/mL, it was 37% as effective as pIgM. A similar study with LNCaP cells showed that only IgG1.kappa. had activity greater than the estrogenic effect seen in

CAPM serum-free defined medium only (FIG. 121). However, in some experiments with prostate cells, IgG2K also showed androgen reversible inhibitory activity (FIG. 122). Based on these studies, it is concluded that IgG1 and IgG2 have small but measurable androgen reversible activity with AR.sup.+ human prostate cancer cells.

The example provide only information obtained in vitro with cancer cell lines and does not address the lack of enablement issues with respect to the level of increase in secretory immunoglobulins over the natural fluctuating level of secretory immunoglobulins in a specimen of bodily fluids or secretions for predicting susceptibility to a estrogen hormone response cancer in a mucosal epithelium which has yet to occur in a subject.

Applicant argues that it is a central premise of the present invention that a long-term decrease in the exposure of epithelial cells exposed to secretory immunoglobulins leads to an increased risk of ,mucosal epithelial cells becoming cancerous. This has been considered but not found persuasive. firstly, the instant claims include an aid to predicting susceptibility based on a single measurement of secretory immunoglobulin, but not require the measurement of secretory immunoglobulins in a subject over a "long term". Secondly, there is no objective evidence that a decrease in the level of secretory immunoglobulin attributable to increased cancer risk can be determined over the natural fluctuation in secretory immunoglobulins because the levels of said immunoglobulins are controlled by a multitude of factors as set forth in the rejection above. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the claimed method.

All other rejections and objections as set forth or maintained in the previous Office action are withdrawn in light of applicants cancellation of the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
01/07/07